Citation for published version:
Busby, J, Murchie, P, Murray, L, Iversen, L, Lee, AJ, Spence, A, Watson, MC & Cardwell, CR 2017, 'The effect of medications which cause inflammation of the gastro-oesophageal tract on cancer risk: a nested case-control study of routine Scottish data', *International Journal of Cancer*, vol. 140, no. 8, pp. 1828-1835. https://doi.org/10.1002/ijc.30612

DOI:
10.1002/ijc.30612

Publication date:
2017

Document Version
Peer reviewed version

Link to publication

This is the peer reviewed version of the following article: The effect of medications which cause inflammation of the gastrooesophageal tract on cancer risk: a nested case–control study of routine Scottish data, International Journal of Cancer, 140/8, 15 April 2017, which has been published in final form at https://doi.org/10.1002/ijc.30612. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

University of Bath

Alternative formats
If you require this document in an alternative format, please contact:
openaccess@bath.ac.uk

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 05. May. 2023

Working Title: The effect of medications which cause inflammation of the gastro-~~esophageal~~oesophageal tract on cancer risk: A nested ~~gastro-esophageal~~oesophageal ~~cancer~~ case-control study of gastro-oesophageal cancer.

Authors (to be confirmed): John Busby, Chris Cardwell, Liam Murray, Peter Murchie, Andy Spence, Lisa Iversen, Amanda J Lee, Mags Watson, Alasdair Coutts etc.

Target Journals: cancer causes and control, pharmacoepidemiology and drug safety, cancer epidemiology, BJC

Word count: 2,092

Abstract

Purpose: Bisphosphonate, tetracyclines and spironolactone use has been shown to increase gastro-~~esophageal~~oesophageal inflammation, an accepted risk factor for cancer. We explore whether use of these medications is associated with an increased risk of gastro-~~esophageal~~oesophageal cancer.

Methods: A nested case-control study was conducted using the Primary Care Clinical Information Unit (PCCIU) database from Scotland. Cases with o~~esophageal~~esophageal or gastric cancer between 1999 and 2011 were matched to up to five controls on age, gender, year of diagnosis and GP practice. Medication use was ascertained using electronic prescribing records. Conditional logistic regression was used to calculate odds ratios (ORs) for the association between medication use and cancer risk after adjustment for potential confounders including medication use and comorbidities.

Results: A slightly higher proportion of gastro-~~esophageal~~oesophageal cancer cases received bisphosphonates (3.9% vs. 3.5%), tetracycline (6.0% vs. 6.0%) and spironolactone (1.4% vs. 1.1%) compared with the controls. The adjusted odds ratios for the association between gastro-~~esophageal~~oesophageal cancer and bisphosphonates, tetracycline and spironolactone were 1.04 (95% CI: 0.84, 1.30), 0.99 (95% CI: 0.83, 1.17) and 1.06 (95% CI: 0.74, 1.51) respectively. Further analysis revealed bisphosphonates were associated with increased o~~esophageal~~esophageal cancer risk (1.33, 95% CI: 1.02, 1.74) and reduced gastric cancer risk (0.69, 95% CI: 0.48, 1.01), although there was no obvious dose-response relationship.

Conclusions: There is little evidence that that the use of bisphosphonate, tetracycline or spironolactone is associated with increased risk of gastro-~~esophageal~~oesophageal cancer. Our findings should provide some reassurance to GPs that these widely-used medications are safe with respect to gastro-~~esophageal~~oesophageal cancer risk.

Commented [LM1]: Is this correct

Introduction

O~~esophageal~~esophageal and gastric cancer are among the most common cancers in the UK with 7,300 and 5,300 new cases diagnosed annually.(1) Prognosis is extremely poor with around 55% of patients dying within one year of diagnosis(2). The role of inflammation in cancer is well established and various mechanisms have been proposed to explain the connection between inflammation and cancer.(3, 4) Several studies have demonstrated that patients with reflux oesophagitis have much higher o~~esophageal~~esophageal cancer risk(5), most likely through the Barrett's pathway.(6, 7) A similar mechanism of cell metaplasia could also account for the marked increase in gastric cancer risk among patients with ulceration.(8, 9)

Bisphosphonates, tetracyclines and spironolactone are widely used medications with main indications of osteoporosis, infections/acne/rosacea and hypertension/cardiac failure, respectively. During 2015, approximately 8.2, 3.2 and 2.5 million were ~~dispensed~~ prescribed by English general practitioners respectively.(10) Long-term usage of these medications is common; for example the anti-fracture effects of some bisphosphonates are only realised after 36 months(11) and tetracycline treatment for acne can last indefinitely.(12) Each of these medications has been associated with increased risk of gastro-~~esophageal~~oesophageal inflammation. Specifically, bisphosphonates have been shown in case reports to cause severe esophagitis including inflammation and thickening of the ~~esophageal~~oesophageal wall(13, 14); more recently the ?US Food and Drug Administration reported 23 cases of ~~esophageal~~oesophageal cancer among bisphosphonate users.(15) Tetracyclines ~~has~~ have also been shown to cause oesophagitis(16, 17) with prospective studies demonstrating an increased risk~~s~~ of ~~oesophageal~~oesophageal injury and ulceration(18), and case reports ~~showing~~ of tetracycline induced lesions.(19) Similarly, spironolactone has been associated with inflammation of the stomach including increased risk of gastric ulcers(20), possibly due to impaired mucosal healing. (20, 21) Despite the widespread and prolonged use of these medications, epidemiological studies have focus~~s~~sed solely on bisphosphonates and gastro-~~esophageal~~oesophageal cancer risk(22), and have yet to ~~assess~~ investigate the ~~impact of~~ risk~~s~~ associated with tetracyclines and spironolactone use.

Therefore, in a case-control study nested within a population-based primary care cohort ~~from~~ in Scotland, we investigated whether bisphosphonates, spironolactone or tetracyclines were associated with an increased risk of gastro-~~esophageal~~oesophageal cancer ~~risk~~.

Commented [IL2]: Think this would be strengthened by a brief international perspective.

Commented [MP3]: Would it be worth giving separate 1-year-mortality rates?

Commented [MP4]: Do you mean that inflammation is well-established as a cause of cancer?

Commented [IL5]: Give an indication of the magnitude of the increased risk.

Commented [MP6]: Like Liam's comment on next sentence – might be better to give a bit more detail about what you mean here

Commented [LM7]: I think that you need to rephrase this and include h.pylori something like. It is well recognised that H. pylori infection causes chronic gastric inflammation that may progress to atrophy, metaplasia, dysplasia, and gastric cancer

Commented [LM8]: I am not sure that you should concentrate on this report and ignore the rash of studies that it spawned

Methods

Data

We conducted a nested case-control study using the Primary Care Clinical Information Unit Research (PCCIUR) database. Between 1993 and 2011, ~~T~~the PCCIUR ~~contains~~ collected computerised medical records from approximately 15% of the Scottish general practice population (over 2 million patients registered with 393 general practices that used the General Practice Administration Systems for Scotland, GPASS clinical system), and includes details on patient demographics (e.g. age, deprivation), primary care encounters, clinical diagnoses and prescriptions (all recorded using Read codes(needs a reference). Our study protocol to access the PCCIUR data was approved by the Research Applications and Data Management Team, University of Aberdeen. Ethical approval for our study was supplied by the Queen's University Belfast, School of Medicine Ethics Committee (reference number: 15.43).

Commented [MP9]: Should probably give a reference – can reference the web-page at http://www.abdn.ac.uk/iahs/research/primary-care/pcciur/background.php

Commented [IL10]: Think more detail about the PCCIU cohort is needed.

Cases and controls

Our primary outcome ~~analysis~~ was ~~for~~ gastro~~-esophageal~~oesophageal cancer (combined) since~~as~~ classifying tumours arising close to the oesophagogastric junction is difficult, and guidance on this process evolved throughout the study period.(23, 24) However, separate site-specific estimates (~~esophageal~~oesophageal and gastric cancer) were also ~~presented~~?calculated. Cases were defined as patients with a first-time ~~esophageal~~oesophageal (Read code: B10..) or gastric (Read code: B11..) cancer diagnosis after 1st January 1999. Up to five controls were randomly selected for each case matched on age, gender, year of diagnosis and GP practice. The index date was defined as the diagnosis date of the case in each matched group. The start of the exposure period was the latest of 1st January 1996 (as prescriptions before this were less likely to be generated electronically) or the date of registration with the GP practice~~ registration~~. Additionally, the exposure period was truncated to ensure it was identical across the matched groups.(25) Cases and controls with an earlier cancer diagnosis (other than non-melanoma skin cancer), and those with less than three years of exposure prior to index date, were excluded.

Commented [LM11]: Need to be consistent with UK or US spelling

Definition of exposure

We identified prescriptions of bisphosphonate, tetracyclines and spironolactone from electronic prescription records. We used the British National Formulary (August 2016 version) to compile a list of proprietary and generic drug names containing these compounds (Appendix 1). We excluded prescriptions before 1st January 1996 and those in the year prior to the index date (to prevent

reverse causation). We defined patients as users if they had at least one prescription during the exposure period. To enable the testing of dose-response relationships we calculated the total number of prescriptions received during the exposure period and split patients into lower (less than the median) and higher (more than the median) users. We conducted a separate analysis for nitrogen-containing bisphosphonates, as these have a more severe impact on oesophagitis, and alendronate, the most commonly prescribed bisphosphonate.

Commented [LM12]: Is there evidence that this is the case – if so reference it

Commented [IL13]: Need references for all of this.

Confounding factors

We identified fourteen comorbidities (myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, connective tissue disease, dementia, chronic obstructive pulmonary disease, rheumatoid arthritis, peptic ulcer disease, diabetes, renal disease, leukaemia / lymphoma, metastatic cancer, liver disease) using ~~GP diagnosis~~ Read codes recorded during the exposure period. Use of aspirin and statins within the exposure period were identified from prescription records (Appendix 1) as associations with ~~oesophageal~~oesophageal and/or gastric cancer have been identified previously.(26, 27) Lifestyle data including body mass index (not obese, obese), smoking status (never, ex, current) and alcohol use (none, low, high) were also available from ~~GP records~~the PCCIUR data.

Commented [MP14]: Pretty sure these were READ codes – worth stating that and including a reference?

Commented [IL15R14]: I agree with this.

Commented [AL16]: Need to include what BMI cutpoint defined obese/non obese

Commented [AL17]: Again using what definition of number of units

Statistical Analysis

We calculated descriptive statistics and ~~comparing~~ compared the demographics and clinical characteristics of the cases and controls. We used conditional logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for the association between medication use and gastro-~~esophageal~~oesophageal cancer. The matched design of the study accounted for the effect of age, gender, general practice and year of diagnosis but additional adjustments were made for the potential confounders of statin use (yes/no), aspirin use (yes/no) and the presence of fourteen comorbidities (yes/no) ~~using regression~~.

Commented [IL18]: Is this shown by the deprivation quintile? If so explain.

Our primary analysis was complete case, however we performed additional sensitivity analysis using multiple imputation with chained equations (MICE) for smoking, alcohol consumption and BMI with age, gender and deprivation used in the imputation, separately for cases and controls, using chained ordered logit models. Briefly, MICE is a simulation-based approach for handling missing data which leads to valid statistical inferences.(28) Sensitivity ~~analysis~~ analyses were also conducted investigating the impact of excluding prescriptions in the two years prior to the index date (as opposed to one defined as ~~in~~ the main analysis) and defining medication users as patients with at

Commented [IL19]: Is this general practice? Be consistent with the terms.

least three prescriptions (as opposed to one in the main analysis). Analyses was conducted using Stata version 13.(29)

Results

We identified 3,098 cases of gastro-~~esophageal~~oesophageal cancer (1,979 ~~oesophageal~~oesophageal and 1,119 gastric cancer) (Table 1). An average of 4.8 controls existed for each case with a mean exposure period of 6.1 years (min 3.0, max 15.1). There were some potentially important differences between cases and controls. Most notably, a larger proportion of cases had a history of peptic ulcer disease (16.7% vs. 9.2%) and COPD (11.7% vs 8.5%), and the cases were much more likely to be current or ex-smokers (64.7% vs 55.3%), drink high levels of alcohol (7.5% vs. 5.3%) and have normal weight (85.8% vs 79.9%). The proportion of missing data for smoking status and alcohol consumption was 21.5% and 32.0% respectively.

~~The main analysis is shown in Table 2.~~ Overall, 3.9% (122/3098) of cases and 3.5% (526/14937) of controls used bisphosphonates suggesting little association between bisphosphonate use and gastro-~~esophageal~~oesophageal cancer risk (adjusted OR= 1.04; 95% CI: 0.84, 1.30) (Table 2). There was evidence of a 33% increased risk (adjusted OR= 1.33; 95% CI: 1.02, 1.74) ~~increased risk~~ of ~~esophageal~~oesophageal cancer in bisphosphonate users but a reduction of 31% (adjusted OR= 0.69; 95% CI: 0.48~~-1~~, 1.01~~52~~) in gastric cancer. The association between bisphosphonates and ~~esophageal~~oesophageal or gastric cancer did not appear to follow a dose-response relationship.

Tetracycline was used by 6.0% (186/3098) of cases and 6.0% (894/14937) of controls and there was no evidence of association with gastro-~~esophageal~~oesophageal cancer risk (OR= 0.99; 95% CI: 0.83, 1.17). Similarly, no significant associations were observed between tetracycline use and ~~esophageal~~oesophageal (OR=1.00; 95% CI: 0.81, 1.24) and gastric cancer (OR=0.97; 95% CI: 0.73, 1.29).

Overall, 1.4% (43/3098) of cases and 1.1% (159/14937) of controls used spironolactone but there was little evidence of association after adjustment for confounders (OR=1.06; 95%: 0.74, 1.51). Again, there was little evidence of higher risk for o~~esophageal~~esophageal or gastric cancer alone, with adjusted odds ratios of 1.07 (95% CI: 0.69, 1.65) and 1.00 (95% CI: 0.52, 1.90) respectively.

In general, our conclusions were little altered in sensitivity analyses shown in Table 3. Similar associations were observed when prescriptions were excluded in the two years prior to diagnosis rather than one (to reduce the risk of reverse causality) and when the exposure definition of 'ever

Commented [IL20]: I'm not sure I agree with this. Yes over the total time period mentioned below there were more gastric cxs than oesophageal cxs but the data show an overall pattern of declining rates of gastric cancer and increasing rates of oesophageal cx. If you look at the Scotland data from 1999 to 2011 (our diagnosis dates), you get a total of 10,721 oesophageal and 10,667 gastric cxs.

Commented [LM21]: There were 20,163 oesophageal cancers diagnosed in Scotland between 1990 and 2014 (inclusive) and 22,103 gastric cancers, so clearly the site distribution in the PCCIU data is wrong – gastric cancers are being diagnosed as oesophageal. This is an argument for examining the associations with gastro-oesophageal cancer as a whole and it means that the site specific estimates are incorrect. It does however weaken the study as we cannot really say anything about the associations with individual sites

Commented [AL22]: Is the distribution of exposure years skewed? If so, need to report median duration of exposure and IQR

Commented [IL23]: Clarify what this actually means.

Commented [LM24]: I think use the proportion obese

AL:agree

Commented [AL25]: Need to be consistent in the way you report the odds ration…either as percentages or proportions

use' was based upon three or more prescriptions rather than one. Additionally, adjusting for lifestyle factors (smoking, alcohol consumption, and obesity), either in a complete case analysis or when using MICE, resulted in similar estimates to the main analysis. We also found slightly larger, although still moderate, associations when restricting our analysis to nitrogen-containing bisphosphonates (OR=1.13; 95% CI: 0.89, 1.44), or alendronate alone (OR=1.11; 95% CI: 0.86, 1.44), compared to the main analysis which combined all bisphosphonates.

Commented [AL26]: Is this the median number of scripts you mentioned earlier?? Be clear that this is the case here and you haven't just picked 3 as a random cut off

Discussion

In this study of ~~oesophageal~~oesophageal and gastric cancer cases and controls in a community-based population, we found little evidence of an association between gastro-~~esophageal~~oesophageal cancer risk and the use of bisphosphonates, tetracyclines or spironolactone. Although there was some evidence that bisphosphonates increased the risk of ~~oesophageal~~oesophageal cancer, there was no obvious dose-response relationship and these increases were largely offset by a reduction in gastric cancer risk.

Strengths and limitations

The main strength of our study lies in the high-quality and nationally representative data on which it is based.(30) It is the first study to investigate the effect of tetracycline and spironolactone on gastro-~~esophageal~~oesophageal cancer risk and has found no evidence of an increased risk, which is important and reassuring given the large numbers of patients who use these medications often for prolonged periods of time.~~could have important implications for clinical practice~~. We used prescribing data collected as part of routine clinical care, in many cases, several years before the onset of ~~esophageal~~oesophageal or gastric cancer which accurately reflects GP prescribing practices and negates the risk of recall bias. Although a weakness~~es~~ of this approach is that we do not know if patients used their prescribed medications, the main conclusions were similar when restricting our analysis to patients who received multiple prescriptions (in which non-compliance is likely to be less of an issue). Our study is observational and hence open to confounding; although we have controlled for many of the key determinants of cancer risk through the matched design and analysis (e.g. age, comorbidities and GP practice) some other risk factors, including ethnicity and nutrition, were not available. Finally, although our study was large, including over 3,000 gastro-~~esophageal~~oesophageal cancers, investigating multiple medications may have increased the possibility of type 2 error.

Comparisons with other research

To our knowledge, this is the first study to investigate the impact of tetracyclines and spironolactone use on gastro-~~esophageal~~oesophageal cancer risk.

Several studies have previously examined the effect of bisphosphonates on gastro-~~esophageal~~oesophageal cancer risk. In agreement with our findings, two UK-based studies which combined the ~~oesophageal~~oesophageal and gastric cancer sites together in a single analysis found no significant association(31, 32) with bisphosphonate use, while another Danish study reported a

Commented [LM27]: Maybe say something here about the misclassification of site

Commented [LM28]: Not sure we should say this, there are not going to be any changes to clinical practice on the basis of this study

Commented [MP29R28]: It's reassuring though especially with tetracyclines, maybe stress that?

Commented [MP30]: Feels like it would be good to strengthen this with some evidence/a reference?

Commented [LM31]: ?

Commented [IL32]: Maybe mention the lack of histological data here?

Commented [AL33]: I don't think this is the case here with only 3 medications investigated……a bigger issue may be due to large numbers involved, small clinical differences may reach statistical significance

Commented [LM34]: ?

37% decrease in risk.(33) Although a recent meta-analysis reported no significant association between bisphosphonate use and ~~oesophageal~~oesophageal cancer risk(22), several individual studies have observed an association. For example, two UK-based studies reported a 30% and 18% increased risk of ~~oesophageal~~oesophageal cancer among bisphosphonate users, which was broadly in line with the 33% effect size estimated in our study.(34, 35) Our finding of reduced gastric cancer incidence among bisphosphonate users was replicated by several other studies(34-36), including one which found a 39% reduction in the risk of gastric cancer(33), although a recent meta-analysis reported no overall effect.(22) Several studies investigating the effect of bisphosphonate use on cancer incidence, separately for both the ~~oesophageal~~oesophageal and gastric sites, reported a similar pattern to our study (i.e. increased risk of ~~oesophageal~~oesophageal cancer which was largely offset by a decreased risk of gastric cancer ~~incidence~~).(34-36)

Implications

Bisphosphonate, tetracycline and spironolactone are widely used and effective treatments for a range of indications including osteoporosis, rosacea and fluid retention. Our study suggests that any inflammation caused by these medications does not substantially increase the risk of gastro-~~esophageal~~oesophageal cancer, and GPs should not be unduly concerned about cancer risk when prescribing these treatments.

It is unclear why bisphosphonate users had an increased risk ~~oesophageal~~ of oesophageal cancer ~~risk~~ in our study. Firstly, these results could represent a true causal association; bisphosphonates are well known to cause dyspepsia and other inflammatory changes (e.g. oesophagitis, mucosal abnormalities)(37) which could form an important part of the upper-gastrointestinal cancer pathway.(15) Perhaps more likely, particularly given our concurrent finding of lower gastric cancer risk among bisphosphonate users, is that these associations are at least partly driven by a form of ascertainment bias. One Danish study reported that, due to higher rates of gastrointestinal side effects, patients receiving bisphosphonates were more than twice as likely to undergo upper endoscopy (4.1% vs. 1.7%).(33) This could lead to earlier detection of ~~oesophageal~~oesophageal cancer, and more accurate classification of some ~~oesophageal~~oesophageal tumours proximal to the oesophagogastric junction in bisphosphonate users, which would have otherwise been incorrectly recorded as gastric in origin.(33)

Commented [LM35]: Is you haven't dealt with the misclassification error earlier you need to discuss it here. It is a bit complex. There is a lot more misclassification than I would have expected. It is likely that the misclassification likely to have occurred in gastric cardia region (the top of the stomach) so it is possible that there is actually an increase in risk in such patients. Have a look at whether any studies have specifically examined bisphosphonates and gastric cardia cancer risk. However, the lack of a dose response argues against a real effect even for this subset of patients

Commented [MP36R35]: Be good to get a view from Alasdair on the mis-classification issue, will email him specifically

Commented [LM37]: Change as in intro

Commented [MP38]: And the public who use them?

Commented [IL39R38]: Yes I agree that patients should be reassured too.

Commented [LM40]: You might need to, at some stage, mention that histological data were not available to allow classification into the two main types of ooesophageal cancer – squamous cell carcinoma and adenocarcinoma

Commented [LM41]: Not sure about this

Conclusions

Overall, our study provided little evidence that the use of bisphosphonate, tetracyclines or spironolactone are associated with increased risk of gastro-~~esophageal~~oesophageal cancer. These findings should provide GPs and patients with some reassurance that these widely-used medications are safe with respect to gastro-~~esophageal~~oesophageal cancer risk.

Commented [MP42]: And the public?

References

1. Office for National Statistics. Cancer Registration Statistics 2014, England 2016 [cited 2016 11/10/2016]. Available from: http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2014.
2. Office for National Statistics. Cancer survival in England: Patients diagnosed between 2010 and 2014 and followed up to 2015 2016 [cited 2016 07/10/2016]. Available from: http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinenglandadultsdiagnosed/2010and2014andfollowedupto2015#5-year-survival.
3. Mantovani A, Marchesi F, Portal C, Allavena P, Sica A. Linking inflammation reactions to cancer: novel targets for therapeutic strategies. Advances in experimental medicine and biology. 2008;610:112-27. PubMed PMID: 18593019. Epub 2008/07/03. Eng.
4. Balkwill FR, Mantovani A. Cancer-related inflammation: common themes and therapeutic opportunities. Seminars in cancer biology. 2012 Feb;22(1):33-40. PubMed PMID: 22210179. Epub 2012/01/03. Eng.
5. Cook MB, Corley DA, Murray LJ, Liao LM, Kamangar F, Ye WM, et al. Gastro-~~esophageal~~oesophageal Reflux in Relation to Adenocarcinomas of the Esophagus: A Pooled Analysis from the Barrett's and ~~Esophageal~~Esophageal Adenocarcinoma Consortium (BEACON). PloS one. 2014 Jul;9(7):11. PubMed PMID: WOS:000340028800056. English.
6. Lassen A, Hallas J, de Muckadell OB. Esophagitis: incidence and risk of ~~esophageal~~oesophageal adenocarcinoma--a population-based cohort study. The American journal of gastroenterology. 2006 Jun;101(6):1193-9. PubMed PMID: 16771936. Epub 2006/06/15. eng.
7. Solaymani-Dodaran M, Logan RF, West J, Card T, Coupland C. Risk of ~~oesophageal~~oesophageal cancer in Barrett's oesophagus and gastro-~~oesophageal~~oesophageal reflux. Gut. 2004 Aug;53(8):1070-4. PubMed PMID: 15247170. Pubmed Central PMCID: PMC1774141. Epub 2004/07/13. eng.
8. Hansson LE, Nyren O, Hsing AW, Bergstrom R, Josefsson S, Chow WH, et al. The risk of stomach cancer in patients with gastric or duodenal ulcer disease. New England Journal of Medicine. 1996 Jul;335(4):242-9. PubMed PMID: WOS:A1996UZ53200004. English.
9. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. Helicobacter pylori infection and the development of gastric cancer. New England Journal of Medicine. 2001 Sep;345(11):784-9. PubMed PMID: WOS:000170906800002. English.
10. Powell-Smith A, Goldacre B. OpenPrescribing.net 2016.
11. Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2008 Jun;19(6):733-59. PubMed PMID: 18214569. Epub 2008/01/25. eng.
12. Dreno B, Bettoli V, Ochsendorf F, Layton A, Mobacken H, Degreef H. European recommendations on the use of oral antibiotics for acne. European journal of dermatology : EJD. 2004 Nov-Dec;14(6):391-9. PubMed PMID: 15564203. Epub 2004/11/27. eng.
13. Ryan JM, Kelsey P, Ryan BM, Mueller PR. Alendronate-induced esophagitis: case report of a recently recognized form of severe esophagitis with ~~esophageal~~oesophageal stricture--radiographic features. Radiology. 1998 Feb;206(2):389-91. PubMed PMID: 9457190. Epub 1998/02/11. eng.
14. de Groen PC, Lubbe DF, Hirsch LJ, Daifotis A, Stephenson W, Freedholm D, et al. Esophagitis associated with the use of alendronate. The New England journal of medicine. 1996 Oct 3;335(14):1016-21. PubMed PMID: 8793925. Epub 1996/10/03. eng.

Commented [MP43]: Sorry! Might have mucked up the reference list with respect to oesophageal and esophageal!

15. Wysowski DK. Reports of ~~Esophageal~~Oesophageal Cancer with Oral Bisphosphonate Use. New England Journal of Medicine. 2009;360(1):89-90. PubMed PMID: 19118315.
16. Zografos GN, Georgiadou D, Thomas D, Kaltsas G, Digalakis M. Drug-induced esophagitis. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus. 2009;22(8):633-7. PubMed PMID: 19392845. Epub 2009/04/28. Eng.
17. Gencosmanoglu R, Kurtkaya-Yapicier O, Tiftikci A, Avsar E, Tozun N, Oran ES. Mid-~~esophageal~~oesophageal ulceration and candidiasis-associated distal esophagitis as two distinct clinical patterns of tetracycline or doxycycline-induced ~~esophageal~~oesophageal injury. Journal of clinical gastroenterology. 2004 Jul;38(6):484-9. PubMed PMID: 15220682. Epub 2004/06/29. Eng.
18. Alvares JF, Kulkarni SG, Bhatia SJ, Desai SA, Dhawan PS. Prospective evaluation of medication-induced ~~esophageal~~oesophageal injury and its relation to ~~esophageal~~oesophageal function. Indian journal of gastroenterology : official journal of the Indian Society of Gastroenterology. 1999 Jul-Sep;18(3):115-7. PubMed PMID: 10407565. Epub 1999/07/17. Eng.
19. Tahan V, Sayrak H, Bayar N, Erer B, Tahan G, Dane F. Doxycycline-induced ulceration mimicking ~~esophageal~~oesophageal cancer. Cases journal. 2008 09/08

07/19/received

09/08/accepted;1:144-. PubMed PMID: PMC2553052.
20. Verhamme K, Mosis G, Dieleman J, Stricker B, Sturkenboom M. Spironolactone and risk of upper gastrointestinal events: population based case-control study. BMJ (Clinical research ed). 2006 Aug 12;333(7563):330. PubMed PMID: 16840442. Pubmed Central PMCID: PMC1539051. Epub 2006/07/15. eng.
21. Doll R, Langman MJ, Shawdon HH. Treatment of gastric ulcer with carbenoxolone: antagonistic effect of spironolactone. Gut. 1968;9(1):42-5. PubMed PMID: PMC1552604.
22. Wright E, Schofield PT, Molokhia M. Bisphosphonates and evidence for association with ~~esophageal~~oesophageal and gastric cancer: a systematic review and meta-analysis. BMJ Open. 2015 December 1, 2015;5(12).
23. Chandrasoma P, Wickramasinghe K, Ma Y, DeMeester T. Adenocarcinomas of the distal esophagus and "gastric cardia" are predominantly ~~esophageal~~oesophageal carcinomas. The American journal of surgical pathology. 2007 Apr;31(4):569-75. PubMed PMID: 17414104. Epub 2007/04/07. eng.
24. Rüdiger Siewert J, Feith M, Werner M, Stein HJ. Adenocarcinoma of the Esophagogastric Junction: Results of Surgical Therapy Based on Anatomical/Topographic Classification in 1,002 Consecutive Patients. Annals of Surgery. 2000;232(3):353-61. PubMed PMID: PMC1421149.
25. Suissa S, Dell'aniello S, Vahey S, Renoux C. Time-window bias in case-control studies: statins and lung cancer. Epidemiology (Cambridge, Mass). 2011 Mar;22(2):228-31. PubMed PMID: 21228697. Epub 2011/01/14. eng.
26. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. Br Med J. 2010 May;340:12. PubMed PMID: WOS:000278061900002. English.
27. Rothwell PM, Fowkes FGR, Belch JFF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011 Jan;377(9759):31-41. PubMed PMID: WOS:000286445200029. English.
28. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Statistics in medicine. 2011 Feb 20;30(4):377-99. PubMed PMID: 21225900. Epub 2011/01/13. eng.
29. StataCorp. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP2013.
30. Elder R, Kirkpatrick M, Ramsay W, Macleod M, Guthrie B, Sutton M, et al. Measuring quality in primary medical services using data from SPICE. 2007.
31. Cardwell CR, Abnet CC, Cantwell MM, Murray LJ. Exposure to oral bisphosphonates and risk of ~~esophageal~~oesophageal cancer. ~~Jama~~JAMA. 2010;304(6):657-63.

32. Wright E, Schofield PT, Seed P, Molokhia M. Bisphosphonates and risk of upper gastrointestinal cancer--a case control study using the General Practice Research Database (GPRD). PloS one. 2012;7(10):e47616. PubMed PMID: 23112825. Pubmed Central PMCID: PMC3480418. Epub 2012/11/01. eng.
33. Abrahamsen B, Pazianas M, Eiken P, Russell RGG, Eastell R. ~~Esophageal~~Oesophageal and gastric cancer incidence and mortality in alendronate users. Journal of Bone and Mineral Research. 2012;27(3):679-86.
34. Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ (Clinical research ed). 2010;341:c4444. PubMed PMID: 20813820. Pubmed Central PMCID: PMC2933354. Epub 2010/09/04. eng.
35. Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to bisphosphonates and risk of gastrointestinal cancers: series of nested case-control studies with QResearch and CPRD data. BMJ (Clinical research ed). 2013 Jan 16;346:f114. PubMed PMID: 23325866. Pubmed Central PMCID: PMC3546625. Epub 2013/01/18. Eng.
36. Lee W-Y, Sun L-M, Lin M-C, Liang J-A, Chang S-N, Sung F-C, et al. A Higher Dosage of Oral Alendronate Will Increase the Subsequent Cancer Risk of Osteoporosis Patients in Taiwan: A Population-Based Cohort Study. PloS one. 2013;7(12):e53032.
37. Parfitt JR, Driman DK. Pathological effects of drugs on the gastrointestinal tract: a review. Human Pathology. 2007 4//;38(4):527-36.

Tables and Figures

Table 1: Characteristics of controls and cases with ~~oesophageal~~oesophageal or gastric cancer

	Cases	Controls
Count	3,098	14,937
At Risk Years (Min, Max)	6.1 (3.0,15.1)	6.1 (3.0,15.1)
Year of Diagnosis		
1999-2003	1,063 (34.3%)	5,151 (34.5%)
2004-2007	1,404 (45.3%)	6,741 (45.1%)
2008-2011	631 (20.4%)	3,045 (20.4%)
Mean Age (SD)	69.6 (11.3)	69.1 (11.2)
0-39	26 (0.8%)	133 (0.9%)
40-59	563 (18.2%)	2,807 (18.8%)
60-79	1,886 (60.9%)	9,269 (62.1%)
80+	623 (20.1%)	2,728 (18.3%)
Sex		
Female	1,095 (35.3%)	5,287 (35.4%)
Male	2,003 (64.7%)	9,650 (64.6%)
Smoking status		
Non-smoker	931 (35.3%)	5,147 (44.7%)
Ex-smoker	898 (34.0%)	3,656 (31.8%)
Current smoker	811 (30.7%)	2,708 (23.5%)
Missing	458	3,426
Alcohol Consumption		
No	551 (24.4%)	2,338 (23.3%)
Low	1,534 (68.1%)	7,145 (71.3%)
High	169 (7.5%)	532 (5.3%)
Missing	844	4,922
Obesity		
Not Obese	2,658 (85.8%)	11,932 (79.9%)
Obese	440 (14.2%)	3,005 (20.1%)
Deprivation Quintile		
1 (Least Deprived)	375 (12.3%)	1,776 (12.0%)
2	555 (18.1%)	2,657 (18.0%)
3	648 (21.2%)	3,137 (21.3%)
4	748 (24.4%)	3,637 (24.6%)
5 (Most Deprived)	734 (24.0%)	3,549 (24.1%)
Missing	38	181
Common Comorbidities[a]		
Connective Tissue Disease	1,377 (44.4%)	6,752 (45.2%)
Peptic Ulcer Disease	518 (16.7%)	1,374 (9.2%)
Diabetes	328 (10.6%)	1,422 (9.5%)
COPD	361 (11.7%)	1,267 (8.5%)
CVD	283 (9.1%)	1,214 (8.1%)
Other Drug Use		
Aspirin	915 (29.5%)	4,217 (28.2%)
Statin	753 (24.3%)	3,367 (22.5%)

[a] For brevity only the 5 most common comorbidities are listed. The full analysis included myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, connective tissue disease, dementia, chronic obstructive pulmonary disease, rheumatoid arthritis, peptic ulcer disease, diabetes, renal disease, leukaemia / lymphoma, metastatic cancer and liver disease

Commented [AL44]: You would normally include a column of p-values in this table to identify which lifestyle factors were statistically significantly different between cases and controls

Commented [AL45]: Need to add definition of low and high in the footnote, also similarly for obese/not obese

Table 2: Combined analysis of drug use risk with ~~oesophageal~~oesophageal and gastric cancer risk

	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]
		Gastro-~~esophageal~~oesophageal combined		
Bisphosphonates				
Never	2,976 (96.1%)	14,411 (96.5%)	Ref	Ref
Ever	122 (3.9%)	526 (3.5%)	1.09 (0.88,1.34)	1.04 (0.84,1.30)
Lower Usage (1-18)	64 (2.1%)	249 (1.7%)	1.22 (0.92,1.61)	1.17 (0.88,1.56)
Higher Usage (19+)	58 (1.9%)	277 (1.9%)	0.97 (0.72,1.31)	0.93 (0.69,1.26)
Tetracycline				
Never	2,912 (94.0%)	14,043 (94.0%)	Ref	Ref
Ever	186 (6.0%)	894 (6.0%)	1.01 (0.86,1.20)	0.99 (0.83,1.17)
Lower Usage (1)	104 (3.4%)	542 (3.6%)	0.93 (0.75,1.16)	0.91 (0.73,1.13)
Higher Usage (2+)	82 (2.6%)	352 (2.4%)	1.14 (0.89,1.45)	1.11 (0.86,1.43)
Spironolactone				
Never	3,055 (98.6%)	14,778 (98.9%)	Ref	Ref
Ever	43 (1.4%)	159 (1.1%)	1.24 (0.88,1.75)	1.06 (0.74,1.51)
Lower Usage (1-10)	21 (0.7%)	77 (0.5%)	1.26 (0.77,2.05)	1.09 (0.66,1.79)
Higher Usage (11+)	22 (0.7%)	82 (0.5%)	1.23 (0.76,1.98)	1.03 (0.63,1.69)
		~~Esophageal~~Oesophageal		
Bisphosphonates				
Never	1,895 (95.8%)	9,254 (97.0%)	Ref	Ref
Ever	84 (4.2%)	289 (3.0%)	1.40 (1.08,1.81)	1.33 (1.02,1.74)
Lower Usage (1-18)	47 (2.4%)	127 (1.3%)	1.78 (1.25,2.51)	1.71 (1.20,2.44)
Higher Usage (19+)	37 (1.9%)	162 (1.7%)	1.09 (0.75,1.58)	1.03 (0.70,1.51)
Tetracycline				
Never	1,858 (93.9%)	8,976 (94.1%)	Ref	Ref
Ever	121 (6.1%)	567 (5.9%)	1.04 (0.85,1.29)	1.00 (0.81,1.24)
Lower Usage (1)	66 (3.3%)	341 (3.6%)	0.95 (0.72,1.24)	0.92 (0.70,1.21)
Higher Usage (2+)	55 (2.8%)	226 (2.4%)	1.19 (0.88,1.61)	1.13 (0.83,1.54)
Spironolactone				
Never	1,949 (98.5%)	9,436 (98.9%)	Ref	Ref
Ever	30 (1.5%)	107 (1.1%)	1.27 (0.84,1.92)	1.07 (0.69,1.65)
Lower Usage (1-10)	13 (0.7%)	55 (0.6%)	1.05 (0.57,1.95)	0.94 (0.50,1.75)
Higher Usage (11+)	17 (0.9%)	52 (0.5%)	1.50 (0.86,2.61)	1.20 (0.67,2.16)
		Gastric		
Bisphosphonates				
Never	1,081 (96.6%)	5,157 (95.6%)	Ref	Ref
Ever	38 (3.4%)	237 (4.4%)	0.72 (0.50,1.04)	0.69 (0.48,1.01)
Lower Usage (1-18)	17 (1.5%)	122 (2.3%)	0.65 (0.39,1.08)	0.62 (0.37,1.05)
Higher Usage (19+)	21 (1.9%)	115 (2.1%)	0.80 (0.49,1.29)	0.77 (0.47,1.25)
Tetracycline				
Never	1,054 (94.2%)	5,067 (93.9%)	Ref	Ref
Ever	65 (5.8%)	327 (6.1%)	0.96 (0.72,1.27)	0.97 (0.73,1.29)
Lower Usage (1)	38 (3.4%)	201 (3.7%)	0.90 (0.63,1.29)	0.90 (0.63,1.30)
Higher Usage (2+)	27 (2.4%)	126 (2.3%)	1.04 (0.68,1.59)	1.09 (0.71,1.68)
Spironolactone				
Never	1,106 (98.8%)	5,342 (99.0%)	Ref	Ref
Ever	13 (1.2%)	52 (1.0%)	1.18 (0.63,2.21)	1.00 (0.52,1.90)
Lower Usage (1-10)	8 (0.7%)	22 (0.4%)	1.78 (0.78,4.08)	1.43 (0.61,3.40)
Higher Usage (11+)	5 (0.4%)	30 (0.6%)	0.75 (0.29,1.98)	0.68 (0.25,1.80)

[b] Adjusted for the presence of myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, connective tissue disease, dementia, chronic obstructive pulmonary disease, rheumatoid arthritis, peptic ulcer disease, diabetes, renal disease, leukaemia / lymphoma, metastatic cancer and liver disease. Additionally conditioned on age, GP practice and year of diagnosis

Commented [LM46]: Need to say that this is number of prescriptions

Table 3: Sensitivity analysis

	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[c]
Bisphosphonates				
2- year exposure lag				
Never	3,001 (96.9%)	14,520 (97.2%)	Ref	Ref
Ever	97 (3.1%)	417 (2.8%)	1.09 (0.86,1.37)	1.03 (0.81,1.31)
Ever use ≥3 prescriptions				
Never	2,988 (96.4%)	14,442 (96.7%)	Ref	Ref
Ever	110 (3.6%)	495 (3.3%)	1.05 (0.84,1.30)	1.00 (0.80,1.25)
MI lifestyle adjusted				
Never	2,976 (96.1%)	14,411 (96.5%)	Ref	Ref
Ever	122 (3.9%)	526 (3.5%)	1.09 (0.88,1.34)	1.03 (0.83,1.27)
Lifestyle complete case				
Never	2,123 (96.0%)	9,218 (96.2%)	Ref	Ref
Ever	88 (4.0%)	369 (3.8%)	1.00 (0.77,1.29)	0.93 (0.71,1.21)
Nitrogen containing bisphosphonates				
Never	3,001 (96.9%)	14,551 (97.4%)	Ref	Ref
Ever	97 (3.1%)	386 (2.6%)	1.18 (0.93,1.50)	1.13 (0.89,1.44)
Alendronate only				
Never	3,015 (97.3%)	14,603 (97.8%)	Ref	Ref
Ever	83 (2.7%)	334 (2.2%)	1.17 (0.91,1.51)	1.11 (0.86,1.44)
Tetracycline				
2- year exposure lag				
Never	2,933 (94.7%)	14,200 (95.1%)	Ref	Ref
Ever	165 (5.3%)	737 (4.9%)	1.10 (0.92,1.31)	1.07 (0.89,1.28)
Ever use ≥3 prescriptions				
Never	3,049 (98.4%)	14,718 (98.5%)	Ref	Ref
Ever	49 (1.6%)	219 (1.5%)	1.10 (0.80,1.50)	1.06 (0.77,1.46)
MI lifestyle adjusted				
Never	2,912 (94.0%)	14,043 (94.0%)	Ref	Ref
Ever	186 (6.0%)	894 (6.0%)	1.01 (0.86,1.20)	1.01 (0.85,1.20)
Lifestyle complete case				
Never	2,067 (93.5%)	8,914 (93.0%)	Ref	Ref
Ever	144 (6.5%)	673 (7.0%)	0.93 (0.76,1.13)	0.91 (0.75,1.12)
Spironolactone				
2- year exposure lag				
Never	3,069 (99.1%)	14,805 (99.1%)	Ref	Ref
Ever	29 (0.9%)	132 (0.9%)	1.02 (0.68,1.53)	0.83 (0.54,1.27)
Ever use ≥3 prescriptions				
Never	3,061 (98.8%)	14,802 (99.1%)	Ref	Ref
Ever	37 (1.2%)	135 (0.9%)	1.26 (0.87,1.83)	1.05 (0.71,1.54)
MI lifestyle adjusted				
Never	3,055 (98.6%)	14,778 (98.9%)	Ref	Ref
Ever	43 (1.4%)	159 (1.1%)	1.24 (0.88,1.75)	1.11 (0.77,1.60)
Lifestyle complete case				
Never	2,175 (98.4%)	9,478 (98.9%)	Ref	Ref
Ever	36 (1.6%)	109 (1.1%)	1.25 (0.83,1.89)	1.15 (0.75,1.77)

[c] Adjusted for the presence of myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, connective tissue disease, dementia, chronic obstructive pulmonary disease, rheumatoid arthritis, peptic ulcer disease, diabetes, renal disease, leukaemia / lymphoma, metastatic cancer and liver disease. Additionally conditioned on age, GP practice and year of diagnosis

Commented [IL47]: Needs more of a description of what the sensitivity analyses are.

Commented [IL48]: Explain what this means

Appendices

Appendix 1: List of generic and proprietary drug names for each exposure and confounder compound

Substance Name	Drug Name
Aspirin	Asasantin, Aspirin, Caprin, Co-codaprin, Micropirin, Migramax, Nu-Seals
Bisphosphonates	Aclasta, Actonel, Alendronic acid, Aredia, Binosto, Bondronat, Bonefos, Bonviva, Clasteon, Clodronate, Didronel, Didronel PMO, Fosamax, Fosavance, Iasibon, Ibrandronic acid, Loron, Pamidronate, Risedronate, Zoledronic acid, Zometa
Spironolactone	Aldactide, Aldactone, Co-flumactone, Lasilactone, Spironolactone
Statin	Atorvastatin, Cholib, Crestor, Dorisin, Fluvastatin, Inegy, Lescol, Lipitor, Lipostat, Luvinsta, Pinmactil, Pravastatin, Rosuvastatin, Simvador, Simvastatin, Stefluvin, Zocor
Tetracycline	Acnamino, Aknemin, Democlocyline, Doxycycline, Doxylar, Efracea, Lymecycline, Minocin, Minocycline, Oxymycin, Oxytetracycline, Sebomin, Tetracycline, Tetralysal, Tigecycline, Tygacil, Vibramycin-D

Appendix 2: Comparison of characteristics for patients with o~~esophageal~~oesophageal and gastric cancer

Commented [AL49]: Do you need to formally test the differences in cases vs controls?

Substance	Oesophagus		Gastric	
	Cases	Controls	Cases	Controls
Count	1,979	9,543	1,119	5,394
At Risk Years (Min, Max)	6.1 (3.0,15.1)	6.1 (3.0,15.1)	6.1 (3.0,14.7)	6.1 (3.0,14.7)
Year of Diagnosis				
1999-2003	665 (33.6%)	3,210 (33.6%)	398 (35.6%)	1,941 (36.0%)
2004-2007	910 (46.0%)	4,382 (45.9%)	494 (44.1%)	2,359 (43.7%)
2008-2011	404 (20.4%)	1,951 (20.4%)	227 (20.3%)	1,094 (20.3%)
Mean Age (SD)	68.8 (11.3)	68.3 (11.1)	71.1 (11.4)	70.6 (11.2)
0-39	10 (0.5%)	52 (0.5%)	16 (1.4%)	81 (1.5%)
40-59	414 (20.9%)	2,070 (21.7%)	149 (13.3%)	737 (13.7%)
60-79	1,207 (61.0%)	5,897 (61.8%)	679 (60.7%)	3,372 (62.5%)
80+	348 (17.6%)	1,524 (16.0%)	275 (24.6%)	1,204 (22.3%)
Sex				
Female	615 (31.1%)	2,975 (31.2%)	480 (42.9%)	2,312 (42.9%)
Male	1,364 (68.9%)	6,568 (68.8%)	639 (57.1%)	3,082 (57.1%)
Smoking				
No	544 (32.3%)	3,232 (43.8%)	387 (40.5%)	1,915 (46.3%)
Ex	578 (34.3%)	2,383 (32.3%)	320 (33.5%)	1,273 (30.7%)
Current	562 (33.4%)	1,756 (23.8%)	249 (26.0%)	952 (23.0%)
Missing	295	2,172	163	1,254
Alcohol Consumption				
No	314 (21.7%)	1,430 (22.2%)	237 (29.3%)	908 (25.3%)
Low	1,005 (69.5%)	4,638 (72.1%)	529 (65.5%)	2,507 (69.9%)
High	127 (8.8%)	363 (5.6%)	42 (5.2%)	169 (4.7%)
Missing	533	3,112	311	1,810
Obesity				
Not Obese	1,703 (86.1%)	7,598 (79.6%)	955 (85.3%)	4,334 (80.3%)
Obese	276 (13.9%)	1,945 (20.4%)	164 (14.7%)	1,060 (19.7%)
Deprivation Quintile				
1 (Least Deprived)	242 (12.4%)	1,141 (12.1%)	133 (12.0%)	635 (11.9%)
2	373 (19.1%)	1,791 (19.0%)	182 (16.4%)	866 (16.2%)
3	406 (20.8%)	1,970 (20.9%)	242 (21.8%)	1,167 (21.8%)
4	464 (23.8%)	2,259 (24.0%)	284 (25.6%)	1,378 (25.8%)
5 (Most Deprived)	466 (23.9%)	2,249 (23.9%)	268 (24.2%)	1,300 (24.3%)
Missing	28	133	10	48
Common Comorbidities[d]				
Connective Tissue Disease	880 (44.5%)	4,281 (44.9%)	497 (44.4%)	2,471 (45.8%)
Peptic Ulcer Disease	289 (14.6%)	880 (9.2%)	229 (20.5%)	494 (9.2%)
Diabetes	197 (10.0%)	922 (9.7%)	131 (11.7%)	500 (9.3%)
COPD	234 (11.8%)	787 (8.2%)	127 (11.3%)	480 (8.9%)
CVD	166 (8.4%)	750 (7.9%)	117 (10.5%)	464 (8.6%)
Other Drug Use				
Aspirin	557 (28.1%)	2,607 (27.3%)	358 (32.0%)	1,610 (29.8%)
Statin	489 (24.7%)	2,124 (22.3%)	264 (23.6%)	1,243 (23.0%)

[d] For brevity only the 5 most common comorbidities are listed. The full analysis included myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, connective tissue disease, dementia, chronic obstructive pulmonary disease, rheumatoid arthritis, peptic ulcer disease, diabetes, renal disease, leukaemia / lymphoma, metastatic cancer and liver disease